

Triosephosphate isomerase deficiency in an infant

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ABSTRACT

Triosephosphate isomerase deficiency is an autosomal recessive disorder characterized by progressive neuromuscular degeneration, seizure, dystonia, weak muscles, cardiomyopathy, hemolytic anemia, and death in early childhood. In the glycolytic pathway, dihydroxy acetone phosphate (DHAP) is converted to glyceraldehyde-3-phosphate by an enzymatic reaction. The reaction is catalyzed by the TPI enzyme. In TPI deficiency, erythrocyte viability is reduced due to insufficient anaerobic respiration and DHAP accumulation causes toxic effects on cells. A 2-month-old boy initially presented with infection and moderate anemia. Respiratory distress and neurological symptoms developed shortly thereafter. He was followed up with a mechanical ventilator for a long time. A homozygous pathogenic variant in the TPI1 gene was detected in the genetic analysis performed due to the progressive neurodegeneration and the need of intermittent erythrocyte transfusion in the follow-up. Here, an infant case with triosephosphate isomerase enzyme deficiency is presented.

Keywords: Triosephosphate isomerase, hemolytic anemia, neurodegeneration

INTRODUCTION

Triosephosphate isomerase (TPI) deficiency, first described in 1965, is an autosomal recessive inherited disease characterized by hemolytic anemia and neurologic impairment, which often leads to death in early childhood (1, 2). TPI enzyme is encoded by the TPI1 gene on chromosome 12p13.31 that maintains the balance between triosephosphates, dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (Ga3P) produced by aldolase in the glycolytic pathway associated with lipid metabolism. Decreased glycolytic flow and related energy impairment, changes in lipid metabolism and conversion of DHAP to toxic methylglyoxal and consequent increase in oxidative stress are expected consequences of TPI deficiency (3, 4). Patients present with severe progressive neuromuscular disorder, cardiomyopathy, susceptibility to infection and mild hemolytic anemia findings. Approximately over 80 variants have been identified to date, and the reported variant was previously reported (5).

We presented an infant diagnosed with triosephosphate isomerase deficiency by genetic study, which were followed up in our clinic with mild anemia and severe psychomotor retardation.

CASE

A 14-month-old male patient was admitted to the hospital at the age of 2 months with fatigue, pallor, and respiratory distress. The patient is the first child of the consanguineous parents. Anemia and leukopenia were detected in the tests, and he was admitted to the ward. On examination, he had decreased turgor tone, hypotonicity, pallor, and chest wall recessions. White blood cell (WBC): $3.65 \times 10^3/\text{mm}^3$, hemoglobin (Hb): 7.5 gr/dl, platelet (Plt): $347 \times 10^3/\text{mm}^3$, lactate dehydrogenase (LDH): 598 U/L, total/direct bilirubin: 0.5/0.3 mg/dl, reticulocyte: 4%, direct agglutinin test (DAT): negative. In peripheral blood smear: erythrocytes had anisocytosis, poikilocytosis, occasional schistocyte and polychromasia (**Figure 1**). With these findings, primarily

non-spherocytic hemolytic anemia was considered. Because he had respiratory distress and moderate anemia (Hb:7.5gr/dl), erythrocyte suspension was transfused. On the 2nd day of his hospitalization, he was intubated and transferred to the intensive care unit (ICU) due to increased respiratory distress and impaired oxygenation. His stay in the ICU was prolonged because his respiratory distress didn't get better. Although sedative drugs were not given, they had decreased neuromotor functions. Two more erythrocyte suspensions were given in the ICU. Since no diagnosis could be made to explain the neuromotor retardation and hemolytic anemia, whole exon sequence analysis was performed. A homozygous c.125G>A pathogenic variant in TPI1 gene associated with triosephosphate isomerase deficiency was detected. In segregation analysis, the parents were observed as heterozygous for this variant. He required frequent erythrocyte transfusions during his two-month ICU stay. A tracheostomy was inserted, and he was discharged with home mechanical ventilator. Nowadays, he is dependent on home mechanical ventilation, and we rarely perform erythrocyte suspension, and symptomatic neurological and physical rehabilitation treatments.

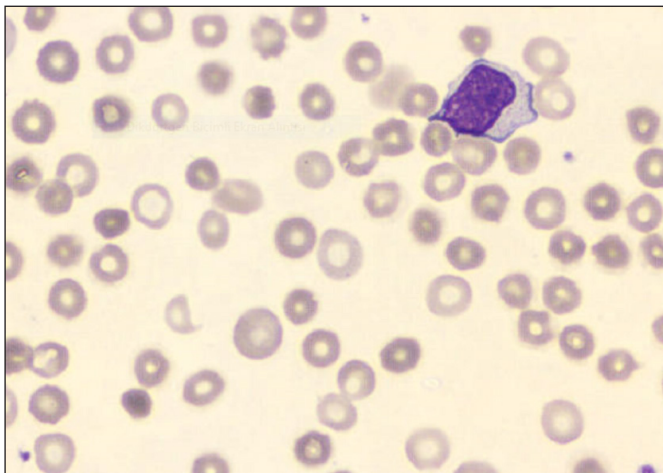


Figure 1. There is anisocytosis, poikilocytosis, increased hemolytic findings like schistocytes.

DISCUSSION

Triosephosphate isomerase (TPI) enzyme was discovered in the 1960s and its deficiency and its relationship with hemolytic anemia were first described by Schneider et al. in 1965 (1, 2). It is an autosomal recessive disease characterized by progressive neuromuscular degeneration, neurological disorders (seizure, hypotonia), cardiomyopathy, hemolytic anemia, and premature death at an early age (about 5 years) (6). It is one of enzymopathies in the glycolytic pathway. However, it differs from others in that it is more severe, progressive, and eventually becomes mortal (7). TPI is encoded by the TPI1 gene on chromosome

12p13.31. Although, the most common mutation is Glu104Asp in TPI1 gene. Cys42Tyr, as in our patient, have been described more rarely in the literature (8). While disease findings are seen in homozygous or compound heterozygous mutations, some studies have shown that the TPI level is reduced by 50% in heterozygous compared to wild type (9).

Disruption of TPI activity does not only affect energy metabolism in erythrocyte. Moreover, it causes accumulation of dihydroxyacetone phosphate and its subsequent chemical conversion to toxic methylglyoxal, resulting in increased toxic effect in neurons, cardiac muscle cells and erythrocytes (4). Although the pathophysiology of hemolytic anemia is easy to understand, the cause of neurological symptoms is not clearly understood. Recent studies show that synaptic vesicular dysfunction is the most important cause of neurological findings (10). Furthermore, Hrizo et al. attribute the neurological symptoms to increased premature mitochondrial dysfunction and increased oxidative stress (11).

Different phenotypes of the disease may be present in the same genetic, as shown in two siblings in a Hungarian family. Although these two siblings have the same variant, one had neurological and hematological findings, while the other one had only hematological findings (12). Neurological symptoms in patients with TPI enzyme deficiency include episodic seizures, dystonia, and progressive hypotonia of the extremities, mental retardation (13). In addition to basic hematological and neurological symptoms, cardiomyopathy and susceptibility to infection are also observed. Eber et al. showed decreased TPI enzyme activity in heart muscle cell and white blood cell (14). Cardiac and infectious complications can be attributed to this pathology. Premature death in early childhood usually occurs due to lower respiratory system infection and following respiratory failure. While the initial finding in TPI deficient patients is usually hemolytic anemia, some patients have only neurological findings dominantly and are followed in neurology clinics.

It is not easy to bring the disease to mind because the symptoms do not occur at the same time and the initial symptom is different for each other. In our patient, severe infection and progressive neurodegenerative findings were prominent with mild hemolytic anemia. The diagnosis can be done by measuring TPI enzyme activity in suspected patients. However, this method may not give accurate result due to frequent transfusion and high enzyme activity in young erythrocytes. Yenicesu et al. detected increased sweet chloride test in a 15-month-old child case. Although different techniques have been tried for diagnosis, they have not been effective (15).

About 80 cases of TPI have been reported so far, due to the rarity of the disease as well as the difficulty of diagnosis (5). In recent years, the diagnosis is made more frequently with the increasing use of whole exome sequencing (WES). We diagnosed our case with WES because of its atypical presentation.

As in other non-immune hemolytic anemia and enzymopathies in the glycolytic pathway, blood transfusion and folate support are given when needed. Due to its susceptibility to severe infection, it is recommended to vaccinate against encapsulated bacteria and seasonal influenza in addition to routine vaccination. Unlike other hemolytic anemias, splenectomy is not recommended due to low life expectancy and increased risk of mortal infection. Mechanical ventilation support may be required due to hypotonicity, weakening of respiratory muscles and diaphragm paralysis. Studies on treatment are ongoing. Conway et al., succeeded in correcting hemolytic anemia with bone marrow transplantation in mice (16). Moreover, Vandemark et al., observed a significant increase in TPI enzyme level in two adult patients diagnosed TPI deficiency (with same compound heterozygous variants: c.315G>C&c.542A>C) with using itavastatin and resveratrol (17).

CONCLUSION

Although treatment options are limited, the chance of survival can be increased with early diagnosis and early interventions. TPI deficiency is a disease that should be kept in mind in children accompanied by signs of hemolytic anemia and neurological symptoms.

ETHICAL STATEMENTS

Informed Consent: Written informed consent was obtained from the patient(s) participating in this study.

Conflict of Interest Status: The authors declared that there was no conflict of interest in this study.

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